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Feature Review

Circadian Rhythms, Sleep, and Disorders of Aging

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Sleep–wake cycles are known to be disrupted in people with neurodegenerative disorders. These findings are now supported by data from animal models for some of these disorders, raising the question of whether the disrupted sleep/circadian regulation contributes to the loss of neural function. As circadian rhythms and sleep consolidation also break down with normal aging, changes in these may be part of what makes aging a risk factor for disorders like Alzheimer's disease (AD). Mechanisms underlying the connection between circadian/sleep dysregulation and neurodegeneration remain unclear, but several recent studies provide interesting possibilities. While mechanistic analysis is under way, it is worth considering treatment of circadian/sleep disruption as a means to alleviate symptoms of neurodegenerative disorders.

Could Age-Associated Changes in Circadian Rhythms and Sleep Contribute to Neurodegenerative Disorders?

Aging is associated with decreased circadian rhythmicity of behaviors including sleep. Age impacts sleep timing, duration, and consolidation, such that overall sleep decreases and also tends to be more fragmented in the elderly. Sleep disruption–- be it shorter sleep duration or poorer sleep quality – is correlated with worsened cognitive performance [1–4]. Aging brings with it a myriad of changes to the brain that may also impact cognitive performance, so it is difficult to isolate the specific effects of sleep and circadian changes. Nevertheless, there is a large and growing body of literature that links changes in the sleep and circadian systems – at the molecular, circuit, and behavioral levels – with normal aging and with diseases of aging such as neurodegenerative disease.

Aging of Central and Peripheral Circadian Systems

Introduction to the Circadian System

The molecular circadian oscillator comprises transcriptional–translational negative feedback loops [5,6]. In the major loop in mammals, the transcription factors BMAL1 and CLOCK heterodimerize during the early circadian day and induce transcription of genes with promoters containing circadian E-box elements. Among these genes are their own negative feedback repressors PERIOD (*Per*) and CRYPTOCHROME (*Cry*) (Figure 1). During the early circadian night, PER and CRY form complexes and repress BMAL1–CLOCK-mediated transcription, thus downregulating their own expression. PER and CRY degrade during the night, releasing negative regulation on BMAL1 and CLOCK and enabling the start of a new circadian day. In an interlocked loop, BMAL1–CLOCK target the expression of the nuclear receptors *rev-erbα* and *ROR*, which in turn inhibit and activate respectively the transcription of BMAL1 to produce cycling of *BMAL1* mRNA. Many other genes also have E-box or REV-ERB/ROR regulatory sequences, so the circadian cycle imposes rhythmic expression on genes involved in many aspects of cellular function [7]. These lead to tissue- and circuit-level oscillations, which ultimately generate overt rhythms of physiology and behavior.

Trends

Sleep and circadian dysfunction are increasingly being associated with neurodegenerative disorders. Earlier studies with human subjects are now supported by findings in genetic models.

Circadian and sleep circuits are damaged in disorders like Huntington's and Parkinson's disease and disrupted sleep/circadian rhythms may exacerbate disease pathology. Thus, these two processes may feed back on each other.

Metabolic factors may provide a mechanistic link between circadian rhythms, sleep, and neurodegenerative disorders.

Sleep and circadian dysregulation could provide a screening tool to identify populations at risk for neurodegenerative disorders.

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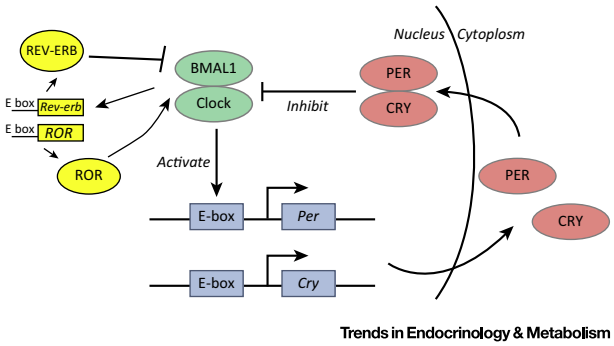

Figure 1. The Circadian Clock. BMAL1 and CLOCK are transcription factors that heterodimerize and bind to E-box element-containing promoters, including promoters for *Per* and *Cry*. PER and CRY form a complex that inhibits BMAL1–CLOCK. In an interlocked loop, BMAL1 and CLOCK target the nuclear receptors REV-ERB and ROR, which feed back to negatively and positively regulate BMAL1 transcription, respectively.

The suprachiasmatic nucleus (SCN) is the central pacemaker of the mammalian circadian system. The SCN contains a heterogeneous population of neuron types [8], including vasoactive intestinal peptide (VIP)-producing neurons in the ventral core and vasopressin (AVP) cells in the dorsal shell. Explanted SCN is capable of maintaining robust circadian rhythmicity for many days *in vitro* [9]. Many other peripheral tissues (e.g., liver, lung, skeletal muscle) are also rhythmic *in vitro* but with oscillations that are much less robust and do not persist as long [9], suggesting that the periphery contains damped oscillators that are entrained by the central SCN.

The role of the SCN as master circadian pacemaker was confirmed by seminal studies using orthotopic SCN transplantation. SCN-lesioned hamsters have permanently disrupted circadian rhythms but those rhythms can be restored by implantation of brain grafts containing fetal SCN [10]. Critical follow-up studies using mutant hamster strains with short circadian periods demonstrated that the period of circadian rhythm is determined by the genotype of the transplant SCN rather than the host [11], establishing the primacy of the SCN in the circadian system. Although the SCN signals circadian information to other brain regions via direct wiring – see below for a discussion on the circuitry relevant to sleep and arousal regions – these transplant studies are powerful evidence that SCN signaling is at least partly via secreted factors. Transplanted SCN does form some synaptic connections with the host brain post-transplantation, but it is unlikely to fully recapitulate the endogenous wiring pattern.

Changes in the Circadian System Seen in Normal Aging

Since the SCN signals both directly and indirectly to numerous brain regions, clock function and aging may be linked by pathology at the level of the SCN, SCN projections, and SCN-secreted signals. In addition, clock activity in other brain regions and in peripheral tissues may change with age.

Although rest–activity rhythms are clearly impaired with age, the core clock in the SCN appears to remain relatively robust despite some age-related changes in expression of individual clock proteins [12–14]. Data are mixed regarding whether aging impairs SCN entrainment to light [15,16]. However, it is clear that peripheral oscillators dampen with age, whether from loss of intrinsic clock function or decline in entraining signals from the SCN, and could contribute to the aging process [17]. Although changes in clock gene expression are still not causally linked to pathology associated with aging, we note that several clock targets are relevant to much of this pathology. For instance, REV-ERBα modulates the expression of genes in several metabolic and inflammatory pathways [18–21]. Also, sirtuins are involved in clock regulation and also in the control of aging [14].

Although the SCN is relatively resistant to age at the level of the molecular clock, it undergoes significant age-related degradation at the network level. The total number of SCN neurons is